

Averaged Electron Densities for Averaged Conformations*

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ABSTRACT: The concepts of averaged electron densities and averaged nuclear arrangements are discussed with reference to small nuclear distortions and an electron density transformation based on the inverse Löwdin transform.
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Introduction

Following the introduction of the molecular electron density quantum similarity measure,^{1–3} several innovative computational approaches have been proposed for the assessment of molecular similarity. Some of these approaches emphasized the fundamental, theoretical aspects involving the basis of quantum chemistry, whereas some others focused on the practical applications in applied fields such as pharmaceutical drug design.^{4–10}

A natural concept related to similarity of molecules, yet one that has not received the degree of attention it seems to deserve, is the concept of average electron density for a family of closely

related electron densities. Such averages are involved in the dynamic analysis of electron densities, in the modeling of active sites of enzymes using information on the shapes of a family of closely related potential substrates, and in crystallographic structure determination problems. Clearly, such an average can be meaningful only if the underlying nuclear arrangements are very similar; for example, the average electron density of a pair of L and D amino acids has very little physical meaning. Here we shall assume that the nuclear arrangements considered deviate from one another only very little, say, of the order of 0.1 Å if optimally superimposed on one another; furthermore, they are distorted versions of the same stable nuclear arrangement. In the terminology of potential energy surface topology, these nuclear arrangements belong to the same catchment region [11]. If the nuclear arrangements deviate only slightly from one another, then electron density transformations designed for small deformations, such as

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the inverse Löwdin transform method,¹²⁻¹⁴ appear as a natural choice for the generation of average electron densities.

In some chemical problems the concept of the (possibly weighted) average of a family of nuclear configurations plays a role. For example, a finite set $\{K_1, K_2, \dots, K_m\}$ of slightly distorted nuclear arrangements of a biomolecule may be used to represent the range of conformations that fit within an enzyme cavity, where distortion may be regarded relative to its minimum energy conformation. The average of these conformations may be interpreted in various ways; for example, one may consider an energy weighting that may assign different probabilistic weights to these conformations, K_1, K_2, \dots, K_m , based on their relative stabilities, or one may scale the displacements by the nuclear masses involved to distinguish the importance and relative roles of heavy and light nuclei. With reference to the configuration space of internal coordinates, one formal average is the conformation, K_{av} , that minimizes the average configuration space distance between K_{av} and the reference conformations K_1, K_2, \dots, K_m . We recall that the internal configuration space is a metric space M with a well-defined distance, but M is not a vector space.¹¹

In many instances, the actual subject of study is the electronic density, and it is of some interest to obtain estimates for the electron density $\rho_{appr}(\mathbf{r}, K_{av})$ of an average conformation K_{av} based on the known electron densities $\rho(\mathbf{r}, K_1), \rho(\mathbf{r}, K_2), \dots, \rho(\mathbf{r}, K_m)$ in conformations K_1, K_2, \dots, K_m . Such problems arise in a variety of computational chemistry fields; for example, when obtaining electron density estimates from a set of known molecular structures for crystallographic structure determination purposes. Such an approach may become useful in studies aimed at the determination of quantum chemical representations from crystallographic experiments in a field called "quantum crystallography."¹⁵ Another natural application may be found in the generation of local electron density models for enzyme cavities based on substrate-enzyme interactions involving several substrates.

In this study one approach to this problem is described, based on the inverse Löwdin transform method also used in the construction of *ab initio* quality macromolecular density matrices,^{12,13} and the computation of approximate macromolecular forces.¹⁴ A method analogous to the inverse Löwdin

transform has been used in quantum crystallography.¹⁵ Here we shall focus on an averaging of the nuclear arrangements with reference to a distinguished configuration, followed by the induced averaging of the electron density.

Average Nuclear Configuration Based on M -Space Distance

For a stoichiometric family of molecules of N nuclei, the $(3N-6)$ -dimensional internal configuration space M (also called the "reduced nuclear configuration space" when used in the context of the $3N$ dimensional mass-weighted Euclidean configuration space ${}^{3N}E$) has a proper metric. This metric $d(K_a, K_b)$ is defined for any pair K_a, K_b of internal configurations of a given stoichiometric family of molecules.¹¹ Besides giving structure to the configuration space M , the metric $d(K_a, K_b)$ also serves as a dissimilarity measure between conformations K_a and K_b . Each actual distance $d(K_a, K_b)$ is derived from the atomic-mass-weighted nuclear coordinates in a laboratory frame. For a system of N nuclei, these mass-weighted nuclear coordinates span the $3N$ -dimensional space ${}^{3N}E$. The quantity (K_a, K_b) is in fact the ${}^{3N}E$ -space distance between equivalence classes of nuclear arrangements in ${}^{3N}E$, related to one another by rigid translation and rotation in the three-dimensional laboratory frame.¹¹

With reference to a family:

$$K = \{K_1, K_2, \dots, K_m\} \quad (1)$$

of nuclear configurations involving the same set of nuclei, the weighted average nuclear configuration K_{av} is chosen as the conformation that minimizes the following sum:

$$s^2(K_{av}, K) = \sum_{i=1, m} w_i d^2(K_{av}, K_i) \quad (2)$$

The quantities w_i are weights for the individual conformations K_i .

To find K_{av} that minimizes $s^2(K_{av}, K)$ of the above formula, a multidimensional optimization is required that is often inconvenient (see Appendix).

A somewhat simpler approach, where the averaging is carried out with respect to a distinguished reference configuration K_0 , requires only a series of six-dimensional optimizations, leading to a K_0 -

biased average, K_{oav} . Although the results of the two approaches, K_{av} and K_{oav} may differ, nevertheless, if the nuclear arrangements K_o and those considered within family K show a high degree of similarity, then the two approaches also lead to similar results. The actual procedure for the generation of K_{oav} is described in the Appendix.

The M -space distance $d(K_o, K_i)$ between K_o and any of the internal configurations K_1, K_2, \dots, K_m is by definition the minimum ${}^{3N}E$ -space distance $\sigma(\mathbf{x}^{(o)}, \mathbf{x}^{(i)})$ between any fixed representative $\mathbf{x}^{(o)}$ of K_o and a representative $\mathbf{x}^{(i)}$ of K_i in ${}^{3N}E$.

Consider a point $\mathbf{x}^{(o)}$ of ${}^{3N}E$ that represents the distinguished reference configuration K_o . The components of point vector $\mathbf{x}^{(o)}$ are the mass-weighted three-dimensional nuclear coordinates, listed according to the serial index assignment of the N nuclei. For the other nuclear arrangements K_1, K_2, \dots, K_m , consider the ${}^{3N}E$ -space representations $\mathbf{x}^{(1)}, \mathbf{x}^{(2)}, \dots, \mathbf{x}^{(m)}$, which realize the minimum distances:

$$\sigma(\mathbf{x}^{(o)}, \mathbf{x}^{(1)}) = d(K_o, K_1) \quad (3)$$

$$\sigma(\mathbf{x}^{(o)}, \mathbf{x}^{(2)}) = d(K_o, K_2), \dots, \quad (4)$$

$$\sigma(\mathbf{x}^{(o)}, \mathbf{x}^{(m)}) = d(K_o, K_m), \quad (5)$$

respectively. Note that the determination of each representative $\mathbf{x}^{(i)}$ involves, at most, the optimization of three translational and three rotational parameters (see Appendix).

A weighted average of the $\mathbf{x}^{(o)}, \mathbf{x}^{(1)}, \mathbf{x}^{(2)}, \dots, \mathbf{x}^{(m)}$ ${}^{3N}E$ -space representations of configurations $K_o, K_1, K_2, \dots, K_m$ is a convex combination of the $\mathbf{x}^{(i)}$ representations, given by:

$$\mathbf{x}^{(oav)} = \sum_{i=0, m} w_i \mathbf{x}^{(i)} \quad (6)$$

where, for the weight factors w_i , the following convexity constraint applies:

$$\sum_{i=0, m} w_i = 1 \quad (7)$$

where $w_i \geq 0$ for each index i .

The ordinary mass-weighted average corresponds to the choice of:

$$w_i = 1/(m+1) \quad (8)$$

for each index i .

Average Electron Density Based on M -Space Distance of Nuclear Configurations and Inverse Löwdin Transforms

If the deviation between the K_{oav} average nuclear configuration and a configuration K_i is small; that is, if their ${}^{3N}E$ -space representations $\mathbf{x}^{(oav)}$ and $\mathbf{x}^{(i)}$ differ only slightly, then a crude but surprisingly good approximation of the electronic density of configuration K_{oav} can be computed very simply, by using the density matrix computed for configuration K_i and a new set of atomic orbitals obtained by simply moving the centers of atomic orbitals $\varphi(\mathbf{x}^{(i)})$ used for K_i to the new nuclear locations on configuration K_{oav} . Specifically, if the difference between $\mathbf{x}^{(oav)}$ and $\mathbf{x}^{(i)}$ is small, then the electronic density $\rho(\mathbf{r}, \mathbf{x}^{(oav)})$ at the displaced nuclear arrangement $\mathbf{x}^{(oav)}$ can be approximated^{13,14,16,17} by taking the density matrix $\mathbf{P}(\mathbf{x}^{(i)})$ and using it with the set of displaced AOs $\varphi_k(\mathbf{r}, \mathbf{x}^{(oav)})$ at the new nuclear locations $\mathbf{x}^{(oav)}$:

$$\rho_{appr}(\mathbf{r}, \mathbf{x}^{(oav)}) = \sum_{k=1}^n \sum_{j=1}^n P_{ij}(\varphi(\mathbf{x}^{(i)})) \times \varphi_k(\mathbf{r}, \mathbf{x}^{(oav)}) \varphi_j(\mathbf{r}, \mathbf{x}^{(oav)}) \quad (9)$$

Although this approach is rather crude, for small displacements the error of the approximate electron density is surprisingly small.

Here we shall follow a technique based on the inverse Löwdin transforms that ensures a better approximation as well as the idempotency of individual transformed density matrices, leading to an average density matrix at the new nuclear geometry $\mathbf{x}^{(oav)}$. The approach followed here is analogous to the method used in Löwdin's orthogonalization technique and related applications.¹⁸⁻²¹

The set of atomic orbital basis functions with centers at the nuclear locations corresponding to the nuclear configuration $\mathbf{x}^{(i)}$ is denoted by the formal vector $\varphi(\mathbf{x}^{(i)})$, with components $\varphi_k(\mathbf{r}, \mathbf{x}^{(i)})$ the individual AO basis functions. The overlap matrix for this set of AOs is denoted by $\mathbf{S}(\mathbf{x}^{(i)})$.

The Löwdin transform of a density matrix $\mathbf{P}(\mathbf{x}^{(i)})$, expressed in terms of the AO basis set $\varphi(\mathbf{x}^{(i)})$, involves pre- and postmultiplication by the matrix $\mathbf{S}(\mathbf{x}^{(i)})^{1/2}$:

$$\mathbf{S}(\mathbf{x}^{(i)})^{1/2} \mathbf{P}(\mathbf{x}^{(i)}) \mathbf{S}(\mathbf{x}^{(i)})^{1/2} \quad (10)$$

Because:

$$\mathbf{P}(\mathbf{x}^{(i)})\mathbf{S}(\mathbf{x}^{(i)})\mathbf{P}(\mathbf{x}^{(i)}) = \mathbf{P}(\mathbf{x}^{(i)}) \quad (11)$$

the Löwdin transform $\mathbf{S}(\mathbf{x}^{(i)})^{1/2}\mathbf{P}(\mathbf{x}^{(i)})\mathbf{S}(\mathbf{x}^{(i)})^{1/2}$ of $\mathbf{P}(\mathbf{x}^{(i)})$ is idempotent with respect to ordinary matrix multiplication:

$$\begin{aligned} & \mathbf{S}(\mathbf{x}^{(i)})^{1/2}\mathbf{P}(\mathbf{x}^{(i)})\mathbf{S}(\mathbf{x}^{(i)})^{1/2}\mathbf{S}(\mathbf{x}^{(i)})^{1/2}\mathbf{P}(\mathbf{x}^{(i)})\mathbf{S}(\mathbf{x}^{(i)})^{1/2} \\ &= \mathbf{S}(\mathbf{x}^{(i)})^{1/2}\mathbf{P}(\mathbf{x}^{(i)})\mathbf{S}(\mathbf{x}^{(i)})^{1/2} \end{aligned} \quad (12)$$

The set of new AO basis functions $\varphi(\mathbf{x}^{(oav)})$ is the set $\varphi(\mathbf{x}^{(i)})$ placed in the new nuclear locations $\mathbf{x}^{(oav)}$. In terms of this new basis set, the overlap matrix $\mathbf{S}(\mathbf{x}^{(oav)})$ is determined. An inverse Löwdin transform of the idempotent matrix $\mathbf{S}(\mathbf{x}^{(i)})^{1/2}\mathbf{P}(\mathbf{x}^{(i)})\mathbf{S}(\mathbf{x}^{(i)})^{1/2}$, generated by the new overlap matrix $\mathbf{S}(\mathbf{x}^{(oav)})$, provides a better approximation of the actual density matrix $\mathbf{P}(\mathbf{x}^{(oav)})$ at the new nuclear geometry $\mathbf{x}^{(oav)}$. This approximation:

$$\begin{aligned} \mathbf{P}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}]) &= \mathbf{S}(\mathbf{x}^{(oav)})^{-1/2}\mathbf{S}(\mathbf{x}^{(i)})^{1/2} \\ &\times \mathbf{P}(\mathbf{x}^{(i)})\mathbf{S}(\mathbf{x}^{(i)})^{1/2}\mathbf{S}(\mathbf{x}^{(oav)})^{-1/2} \end{aligned} \quad (13)$$

is also idempotent with respect to multiplication through the actual overlap matrix $\mathbf{S}(\mathbf{x}^{(oav)})$:

$$\begin{aligned} & \mathbf{P}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}])\mathbf{S}(\mathbf{x}^{(oav)})\mathbf{P}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}]) \\ &= \mathbf{P}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}]) \end{aligned} \quad (14)$$

as this can be easily verified by substitution.

The overall transformation of $\mathbf{P}(\mathbf{x}^{(i)})$ into the new density matrix $\mathbf{P}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}])$ is analogous to an "orthonormalization-deorthonormalization" process that is using the original and displaced basis sets at the two nuclear geometries, $\mathbf{x}^{(i)}$ and $\mathbf{x}^{(oav)}$, respectively.

An approximate electron density $\rho_{appr}(\mathbf{r}, \mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}])$ can be computed for the nuclear geometry $\mathbf{x}^{(oav)}$, based on the electron density computed at the nuclear geometry $\mathbf{x}^{(i)}$, using the following expression:

$$\begin{aligned} & \rho_{appr}(\mathbf{r}, \mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}]) \\ &= \sum_{k=1}^n \sum_{j=1}^n P_{kj}(\mathbf{x}^{(oav)}, \\ &\times [\mathbf{x}^{(i)}]) \varphi_k(\mathbf{r}, \mathbf{x}^{(oav)}) \varphi_j(\mathbf{r}, \mathbf{x}^{(oav)}) \end{aligned} \quad (15)$$

This approximate electron density is based on the idempotent approximation $\mathbf{P}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}])$ of the density matrix $\mathbf{P}(\mathbf{x}^{(oav)})$. The actual computation

involves only the density matrix $\mathbf{P}(\mathbf{x}^{(i)})$ at nuclear geometry $\mathbf{x}^{(i)}$ and basis set information.

If electron densities (density matrices) are available for several nuclear arrangements similar to the arrangement $\mathbf{x}^{(oav)}$, then one may expect that a more reliable approximation can be obtained for the actual electron density $\rho(\mathbf{r}, \mathbf{x}^{(oav)})$ of nuclear configuration $\mathbf{x}^{(oav)}$. Let us assume that for the entire family of nuclear configurations $\mathbf{x}^{(o)}, \mathbf{x}^{(1)}, \mathbf{x}^{(2)}, \dots, \mathbf{x}^{(m)}$, the same type of basis set is used in the computation of the corresponding electron densities $\rho(\mathbf{r}, \mathbf{x}^{(o)})$, $\rho(\mathbf{r}, \mathbf{x}^{(1)})$, $\rho(\mathbf{r}, \mathbf{x}^{(2)})$, \dots , $\rho(\mathbf{r}, \mathbf{x}^{(m)})$, and the only difference among these basis sets is small displacements of the nuclear centers. A simple, weighted average of the approximate electron densities $\rho_{appr}(\mathbf{r}, \mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}])$ for the entire range of indices $i = 0, 1, 2, \dots, m$ can be generated:

$$\rho^{(oav)}(\mathbf{r}, \mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\}) = \sum_{i=1}^m w_i \rho_{appr}(\mathbf{r}, \mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}]) \quad (16)$$

where the weights w_i are the same as those in eq. (6), subject to the convexity condition, eq. (7).

Because the final nuclear locations $\mathbf{x}^{(oav)}$ are common for each of the nuclear geometry displacements from $\mathbf{x}^{(i)}$ to $\mathbf{x}^{(oav)}$, expression (16) leads to local electron density maxima at the same nuclear centers, and to an averaged, approximate electron density that is a realistic representation of the actual electron density at the nuclear geometry $\mathbf{x}^{(oav)}$.

Representation of Average Electron Density by a Single Approximate Density Matrix

The average electron density $\rho_{oav}(\mathbf{r}, \mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\})$, determined from a set of electron densities (density matrices) of similar nuclear geometries using the simple relation eq. (16), can also be expressed in terms of a single approximate density matrix.

To show this, note that if one applies transformation (13) to each of the density matrices $\mathbf{P}(\mathbf{x}^{(o)}), \mathbf{P}(\mathbf{x}^{(1)}), \mathbf{P}(\mathbf{x}^{(2)}), \dots, \mathbf{P}(\mathbf{x}^{(m)})$, the final basis set $\varphi(\mathbf{x}^{(oav)})$ is common in each transformation. Furthermore, for each index i , the expression for the approximate electron density in terms of the idempotent density matrix $\mathbf{P}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}])$, given in eq. (15) is linear in the density matrix elements $P_{kj}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}])$. Consequently, the weighted aver-

age $\rho^{(oav)}(\mathbf{r}, \mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\})$ of all the $m + 1$ approximate electron densities obtained at the average nuclear geometry $\mathbf{x}^{(oav)}$, based on the various reference nuclear geometries, can be rearranged:

$$\begin{aligned} \rho^{(oav)}(\mathbf{r}, \mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\}) &= \sum_{i=1}^m w_i \sum_{k=1}^n \sum_{j=1}^n \\ &\quad \times P_{kj}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}]) \varphi_k(\mathbf{r}, \mathbf{x}^{(oav)}) \varphi_j(\mathbf{r}, \mathbf{x}^{(oav)}) \\ &= \sum_{k=1}^n \sum_{j=1}^n \sum_{i=1}^m w_i P_{kj}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}]) \\ &\quad \times \varphi_k(\mathbf{r}, \mathbf{x}^{(oav)}) \varphi_j(\mathbf{r}, \mathbf{x}^{(oav)}) \\ &= \sum_{k=1}^n \sum_{j=1}^n P^{(oav)}_{kj}(\mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\}) \\ &\quad \times \varphi_k(\mathbf{r}, \mathbf{x}^{(oav)}) \varphi_j(\mathbf{r}, \mathbf{x}^{(oav)}) \end{aligned} \quad (17)$$

where the approximate density matrix $\mathbf{P}^{(oav)}(\mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\})$ is defined as the following weighted average:

$$\mathbf{P}^{(oav)}(\mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\}) = \sum_{i=1}^m w_i \mathbf{P}(\mathbf{x}^{(oav)}, [\mathbf{x}^{(i)}]). \quad (18)$$

The above approximate density matrix expression is advantageous, because it circumvents the somewhat tedious and memory-bound numerical averaging of electron densities at three-dimensional grid points. Once the average density matrix $\mathbf{P}^{(oav)}(\mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\})$ is calculated, the average electron density can be obtained from eq. (17) as:

$$\begin{aligned} \rho^{(oav)}(\mathbf{r}, \mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\}) &= \sum_{k=1}^n \sum_{j=1}^n P^{(oav)}_{kj}(\mathbf{x}^{(oav)}, \\ &\quad \cdot \{\mathbf{x}^{(i)}\}) \varphi_k(\mathbf{r}, \mathbf{x}^{(oav)}) \varphi_j(\mathbf{r}, \mathbf{x}^{(oav)}). \end{aligned}$$

Consistency and Limit Behavior

In the limit of coincident nuclear geometries, the average density matrix $\mathbf{P}^{(oav)}(\mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\})$ and the average electron density $\rho^{(oav)}(\mathbf{r}, \mathbf{x}^{(oav)}, \{\mathbf{x}^{(i)}\})$ become the idempotent density matrix $\mathbf{P}(\mathbf{x}^{(o)})$ and the reference electron density $\rho(\mathbf{r}, \mathbf{x}^{(o)})$, respectively, as a simple consequence of the construction of these averages.

Appendix

A brief review of the determination of M -space distances and the representative ${}^{3N}E$ -space configurations is given, following the treatment and notations of ref. 11. For more details, the reader may consult ref. 11.

The laboratory-frame Cartesian coordinates of a nucleus of index a are denoted by:

$$A_{a1} = X_a \quad (19)$$

$$A_{a2} = Y_a \quad (20)$$

and

$$A_{a3} = Z_a, \quad a = 1, 2, \dots, N. \quad (21)$$

These numbers can be ordered into a $(3N)$ -dimensional vector q :

$$\mathbf{q}' = (X_1, Y_1, Z_1, X_2, \dots, Z_N). \quad (22)$$

For a proper description of some dynamic properties it is convenient to scale these coordinates by the square roots of nuclear masses, leading to the so-called *mass-weighted Cartesian coordinates*, given by:

$$x_i = m_a^{1/2} q_i \quad (23)$$

where:

$$a = [(i - 1)/3] + 1 \quad (24)$$

and where the square bracket $[t]$ represents the largest integer not exceeding the value t (*entier* function).

These x_i components span a $(3N)$ -dimensional Euclidean nuclear configuration space ${}^{3N}E$, where each point represents a nuclear configuration if one assumes pointlike nuclei. Different points may represent the same internal configuration. If nuclear geometries related to one another by rigid translations and rigid rotations within the laboratory frame are regarded as equivalent, then space ${}^{3N}E$ can be partitioned into equivalence classes.

Consider the ${}^{3N}E$ space effects of a rigid translation of the molecule within the laboratory frame, an initial nuclear arrangement represented by point $\mathbf{x} \in {}^{3N}E$, and translations of the molecule parallel to the X , Y , and Z laboratory-frame coordinate axes by a *unit distance*. This leads to the new

points $\mathbf{x}^{(X)}$, $\mathbf{x}^{(Y)}$, and $\mathbf{x}^{(Z)} \in {}^{3N}E$, respectively, given as:

$$\mathbf{x}^{(X)} = \mathbf{x} + \mathbf{y}^{(X)} \quad (25)$$

$$\mathbf{x}^{(Y)} = \mathbf{x} + \mathbf{y}^{(Y)} \quad (26)$$

and:

$$\mathbf{x}^{(Z)} = \mathbf{x} + \mathbf{y}^{(Z)} \quad (27)$$

where the vectors $\mathbf{y}^{(X)}$, $\mathbf{y}^{(Y)}$, and $\mathbf{y}^{(Z)} \in {}^{3N}E$ are defined as:

$$\mathbf{y}^{(X)} = (m_1^{1/2}, 0, 0, m_2^{1/2}, 0, 0, \dots, m_N^{1/2}, 0, 0)' \quad (28)$$

$$\mathbf{y}^{(Y)} = (0, m_1^{1/2}, 0, 0, m_2^{1/2}, 0, \dots, 0, m_N^{1/2}, 0)' \quad (29)$$

and:

$$\mathbf{y}^{(Z)} = (0, 0, m_1^{1/2}, 0, 0, m_2^{1/2}, \dots, 0, 0, m_N^{1/2})' \quad (30)$$

respectively.

An arbitrary translation in the laboratory frame corresponds to a ${}^{3N}E$ -space displacement confined to a three-dimensional hyperplane L_x of ${}^{3N}E$. Hyperplane L_x contains the initial point \mathbf{x} , and is spanned by the three vectors $\mathbf{y}^{(X)}$, $\mathbf{y}^{(Y)}$, and $\mathbf{y}^{(Z)}$; that is:

$$L_x = \{\mathbf{x}': \mathbf{x}' = \mathbf{x} + \beta_X \mathbf{y}^{(X)} + \beta_Y \mathbf{y}^{(Y)} + \beta_Z \mathbf{y}^{(Z)}\} \quad (31)$$

for any $\mathbf{x} \in {}^{3N}E$. The β_X , β_Y , and β_Z parameters can take any real value:

$$-\infty \leq \beta_X, \beta_Y, \beta_Z \leq \infty \quad (32)$$

For notational convenience, we define a general translation operator $\mathbb{Y}(\beta)$ as:

$$\mathbb{Y}(\beta)\mathbf{x} = \mathbb{Y}_1(\beta_1)\mathbb{Y}_2(\beta_2)\mathbb{Y}_3(\beta_3)\mathbf{x} \quad (33)$$

where individual translation operators $\mathbb{Y}_i(\beta_i)$ are defined by:

$$\mathbb{Y}_i(\beta_i)\mathbf{x} = \mathbf{x} + \beta_i \mathbf{y}^i, \quad i = 1, 2, 3 \quad (34)$$

and where indices $i = 1, 2$, and 3 are assigned to the laboratory-frame coordinate axes X , Y , and Z , respectively.

In eq. (33), the three-dimensional vector β is defined by:

$$\beta' = (\beta_1, \beta_2, \beta_3) \quad (35)$$

Note that, in the laboratory frame, the overall effects of an arbitrary displacement of a rigid molecule, that is, an arbitrary translation combined with a rotation about an arbitrary axis by an angle, can always be reproduced by some transla-

tion followed by three subsequent rotations by some angles about the Cartesian axes of the laboratory frame. For a nuclear arrangement corresponding to point $\mathbf{x} \in {}^{3N}E$, the ${}^{3N}E$ -space effects of any translation can be described within the hyperplane L_x ; therefore, the description of the ${}^{3N}E$ -space effects of laboratory-frame rotations about the laboratory-frame Cartesian axes is the only additional step required for the description of any arbitrary displacement.

A ${}^{3N}E$ -space rotation matrix $\mathbb{T}_W(\Theta_W)$ corresponding to a laboratory frame rotation about coordinate axes W by angle Θ_W ($W = X, Y$, or Z) is block diagonal with 3×3 blocks, where each block represents a three-dimensional rotation of an individual nucleus. As in the case of translations, we assign the index values $j = 1, 2, 3$ to the laboratory-frame coordinate axes X, Y, Z , respectively, and write for the general matrix element of the rotation matrix $\mathbb{T}_j(\Theta_j)$:

$$\begin{aligned} (\mathbb{T}_j(\Theta_j))_{rp} = & \delta_{rp}(\cos \Theta_j + (1 - \cos \Theta_j)\delta_{kq}) \\ & + (\sin \Theta_j)\{\delta_{1j}(\delta_{rp+1}\delta_{0q} - \delta_{r+1p}\delta_{0s}) \\ & + \delta_{2j}(\delta_{rp+2}\delta_{0q} - \delta_{r+2p}\delta_{0s}) \\ & + \delta_{3j}(\delta_{rp+1}\delta_{2q} - \delta_{r+1p}\delta_{2s})\} \end{aligned} \quad (36)$$

where:

$$k = j \bmod 3 \quad (37)$$

$$q = r \bmod 3 \quad (38)$$

$$s = p \bmod 3 \quad (39)$$

and:

$$0 \leq \Theta_j < 2\pi, \quad j = 1, 2, 3 \quad (40)$$

We use the notation $\mathbb{T}(\Theta)$ for the operation equivalent to three subsequent rotations about laboratory-frame axes Z , Y , and X by angles Θ_3 , Θ_2 , and Θ_1 , respectively:

$$\mathbb{T}(\Theta)\mathbf{x} = \mathbb{T}_1(\Theta_1)\mathbb{T}_2(\Theta_2)\mathbb{T}_3(\Theta_3)\mathbf{x} \quad (41)$$

where the three-dimensional vector Θ is defined by:

$$\Theta' = (\Theta_1, \Theta_2, \Theta_3) \quad (42)$$

Two points, $\mathbf{x}^{(1)}$ and $\mathbf{x}^{(2)}$, of Euclidean nuclear configuration space ${}^{3N}E$ represent the same internal configuration of the nuclei if and only if there exist parameter vectors Θ and β , such that:

$$\mathbf{x}^{(2)} = \mathbb{T}(\Theta)\mathbb{Y}(\beta)\mathbf{x}^{(1)} \quad (43)$$

Consequently, the $\mathbb{T}(\Theta)$ and $\mathbb{Y}(\beta)$ transformations generate an equivalence class decomposition of space ${}^{3N}E$, where the equivalence classes K_α are defined by the following equivalence relation **ty**:

$$\mathbf{x}^{(1)}\mathbf{ty}\mathbf{x}^{(2)} \quad (44)$$

if and only if there exists vector pair Θ and β such that eq. (43) holds.

Each internal nuclear configuration of the molecular system corresponds to one and only one equivalence class K_α . Except for colinear nuclear geometries, each equivalence class K_α is a six-dimensional subset of the Euclidean nuclear configuration space ${}^{3N}E$. For a discussion of special cases of lower dimensions, see ref. 11.

The K_α equivalence classes form the basis of a rather general internal configuration space for the description of the internal motions of molecules.¹¹ The $(3N-6)$ -dimensional *metric space*, denoted by M , is the *quotient space* generated from the Euclidean nuclear configuration space ${}^{3N}E$ by equivalence relation (44).

A proper distance function, that is, a *metric* $d(K_\alpha, K_\tau)$, can be defined in the internal configuration space M .¹¹ This metric is given in terms of the natural, Euclidean metric $\sigma(\mathbf{x}, \mathbf{x}')$ of the space ${}^{3N}E$, and is defined as:

$$d(K_\alpha, K_\tau) = \min\{\sigma(\mathbf{x}^{(\alpha)}, \mathbf{x}^{(\tau)}): \mathbf{x}^{(\alpha)} \in K_\alpha, \mathbf{x}^{(\tau)} \in K_\tau\} \quad (45)$$

As has been shown,¹¹ one of the ${}^{3N}E$ -space representatives of the two conformations, say $\mathbf{x}^{(\alpha)} \in K_\alpha$, may be kept fixed, and the actual minimization can be restricted to finding the optimum choice of the other representative, $\mathbf{x}^{(\tau)} \in K_\tau$. This implies that the minimization can be carried out by optimizing parameter vectors Θ and β in the following expression:

$$\mathbf{x}^{(\tau)} = \mathbb{T}(\Theta)\mathbb{Y}(\beta)\mathbf{x}^{(\tau')} \quad (46)$$

where $\mathbf{x}^{(\tau')} \in K_\tau$ is any fixed representative of internal configuration K_τ .

Because the total number of the degrees of freedom in parameter vectors Θ and β is 6, the determination of M -space distance and the identification of a laboratory-frame configuration that realizes this actual distance in the space ${}^{3N}E$ requires a six-dimensional optimization. Because in our problems the nuclear geometries are assumed to be rather similar, this optimization is not expected to represent a significant computational problem.

These considerations apply to the generation of the K_o -biased average conformation K_{oav} . Specifically, the generation of K_{oav} involves the determination of m distances $\sigma(\mathbf{x}^{(o)}, \mathbf{x}^{(i)}) = d(K_o, K_i)$, $i = 1, 2, \dots, m$, that can be accomplished in m six-dimensional optimizations.

Note, however, that the determination of the weighted average nuclear configuration K_{av} that minimizes the sum:

$$s^2(K_{av}, K) = \sum_{i=1, m} w_i d^2(K_{av}, K_i)$$

involves additional optimizations, because for each iterative approximation $K_{av}(i)$ to K_{av} , where i is the index of iteration, all distances $d(K_{av}, K_i)$ must be re-evaluated in each iterative step. This feature of the determination of K_{av} is a considerable disadvantage, hence the simpler and computationally feasible K_o -biased average conformation K_{oav} is the recommended alternative.

Acknowledgments

“Schrödinger found the quantum-mechanical Schrödinger equation; Allinger solved the molecular-mechanical Allinger equation.”

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